

# Randomized Clinical Trial of Therapeutic Exercise in Subacute Stroke

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**Background and Purpose**—Rehabilitation care after stroke is highly variable and increasingly shorter in duration. The effect of therapeutic exercise on impairments and functional limitations after stroke is not clear. The objective of this study was to determine whether a structured, progressive, physiologically based exercise program for subacute stroke produces gains greater than those attributable to spontaneous recovery and usual care.

**Methods**—This randomized, controlled, single-blind clinical trial was conducted in a metropolitan area and 17 participating healthcare institutions. We included persons with stroke who were living in the community. One hundred patients (mean age, 70 years; mean Orpington score, 3.4) consented and were randomized from a screened sample of 582. Ninety-two subjects completed the trial. Intervention was a structured, progressive, physiologically based, therapist-supervised, in-home program of thirty-six 90-minute sessions over 12 weeks targeting flexibility, strength, balance, endurance, and upper-extremity function. Main outcome measures were postintervention strength (ankle and knee isometric peak torque, grip strength), upper- and lower-extremity motor control (Fugl Meyer), balance (Berg and functional reach), endurance (peak aerobic capacity and exercise duration), upper-extremity function (Wolf Motor Function Test), and mobility (timed 10-m walk and 6-minute walk distance).

**Results**—In the intention-to-treat multivariate analysis of variance testing the overall effect, the intervention produced greater gains than usual care (Wilk's  $\lambda=0.64$ ,  $P=0.0056$ ). Both intervention and usual care groups improved in strength, balance, upper- and lower-extremity motor control, upper-extremity function, and gait velocity. Gains for the intervention group exceeded those in the usual care group in balance, endurance, peak aerobic capacity, and mobility. Upper-extremity gains exceeded those in the usual care group only in patients with higher baseline function.

**Conclusions**—This structured, progressive program of therapeutic exercise in persons who had completed acute rehabilitation services produced gains in endurance, balance, and mobility beyond those attributable to spontaneous recovery and usual care. (*Stroke*. 2003;34:2173-2180.)

**Key Words:** exercise ■ outcome ■ rehabilitation

Stroke is the leading cause of major disability in older Americans and the largest consumer of rehabilitation services.<sup>1</sup> The duration of acute rehabilitation hospital stays has decreased so that recovery is often not complete at discharge.<sup>2</sup> Therapy in the postacute phase of stroke recovery may increase the likelihood of further improvement.<sup>3-7</sup>

Although most motor and functional recovery occurs in the first 3 months after stroke,<sup>8-10</sup> evidence for the effectiveness of therapeutic exercise programs has been generated in individuals with chronic stroke in whom benefits to motor control, strength, upper-extremity use, mobility, balance, and aerobic capacity have been found.<sup>11-17</sup> Although exercise programs developed in research settings are usually task

specific and intensive and require progression of difficulty, programs in clinical practice are variable and characterized by multiple, conflicting, and unsubstantiated treatment philosophies.<sup>18,19</sup> Therapy in clinical practice often lasts only a few weeks and lacks progression in intensity and task complexity.

Although stroke causes problems across multiple systems, including motor control, upper-extremity function, balance, gait, and endurance, most stroke rehabilitation research has focused on only 1 or 2 dimensions of stroke impairments or functions. No study to date has incorporated multiple components (strength, balance, endurance, and upper-extremity function) into a comprehensive intervention for individuals

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during the recovery phase of stroke. The purpose of this study is to determine the effect of a structured, reproducible, physiologically based, progressive exercise program on strength, balance, endurance, and upper-extremity function after stroke. We designed a randomized, controlled, single-blind clinical trial comparing the intervention program to usual care. We targeted stroke survivors who had mild to moderate persistent deficits, had completed acute rehabilitation services, and were 1 to 4 months after the stroke event.

## Methods

### Design

This is a prospective, randomized, single-blind, clinical intervention trial. Informed consent was given by all subjects through methods approved by the university Institutional Review Board and each participating facility. Subjects were recruited from an ongoing stroke registry. On the basis of estimates from a pilot study,<sup>11</sup> this study had power of >99% to detect a difference in mobility outcomes.

### Subjects

Candidates for the study were selected from the Kansas City Stroke Registry, which had 17 participating medical facilities. All subjects recruited into the registry signed an informed consent and gave permission to be screened for eligibility for future research studies including the present study. A stroke case was defined according to the World Health Organization definition as "rapid onset of an event of vascular origin, reflecting a focal disturbance of cerebral function, excluding isolated impairments of higher function and persisting longer than 24 hours."<sup>20</sup> Diagnosis was confirmed by clinical assessment and/or a positive CT/MRI scan. Eligibility for the registry also required age >50, stroke onset within 3 to 28 days, and residence within a 50-mile radius. Persons were excluded if they had a subarachnoid hemorrhage; were lethargic, obtunded, or comatose; had uncontrolled blood pressure, hepatic or renal failure, NYHA III/IV heart failure, known limited life expectancy, or prestroke disability in self care; or lived in a nursing home prior to the stroke.

Participants from the registry were eligible to be screened for the clinical trial. Inclusion criteria for the trial were the following: (1) stroke within 30 to 150 days; (2) ability to ambulate 25 ft independently; (3) mild to moderate stroke deficits defined by a Fugl-Meyer score of 27 to 90 for upper and lower extremities, an Orpington Prognostic Scale score of 2.0 to 5.2, and palpable wrist extension on the involved side; and (4) Folstein Mini-Mental Status examination score  $\geq 16$ . Exclusions were (1) serious cardiac conditions (hospitalization for heart disease within 3 months, active angina serious cardiac arrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, pulmonary embolus, or infarction), (2) oxygen dependence, (3) severe weight-bearing pain, (4) other serious organ system disease, and (5) life expectancy of <1 year. After subjects passed the screening criteria, they signed an informed consent to participate in this study. Each subject's primary care physician approved participation in the study.

## Measures

### Stroke Severity

Stroke severity was assessed with the Orpington Prognostic Scale, a brief screen of upper-extremity motor function, proprioception, balance, and cognition.<sup>21</sup> It is reliable, valid, and predictive of 3-month stroke-related outcomes.<sup>22</sup>

### Motor Recovery and Strength

The Fugl-Meyer Motor Score<sup>23</sup> assesses stroke motor recovery and has a range of 0 to 66 for the upper extremity and 0 to 34 for the lower extremity. The Wolf Motor Function Test is a 15-item measure of timed functional use of the upper extremity.<sup>24</sup> Grip strength was measured with a JAMAR dynamometer to the nearest kilogram.<sup>25</sup> Isometric strength testing for ankle dorsiflexion and knee extension

was assessed with a Cybex dynamometer.<sup>26</sup> Each joint was fixed at a specific angle (10° plantar flexion at the ankle, 60° flexion at the knee).

### Gait and Balance

The 10-Meter Walk is a measure of gait velocity.<sup>27</sup> The Six-Minute Walk<sup>28</sup> assesses distance covered in response to a request to cover as much distance as possible. Subjects were allowed to stop and rest as necessary. The Berg Balance Scale consists of 14 tasks and a score range of 0 to 56.<sup>29</sup> Functional reach is a brief measure of balance.<sup>30</sup>

### Exercise Stress Test

After consent and with primary physician approval, participants were screened by the study cardiologist for cardiac safety before the baseline bicycle exercise test. No changes in medications were made for the test. The exercise protocol was modified from Potempa et al.<sup>16</sup> In summary, the subject started pedaling at 60 rpm and 0 W, and workload was increased by 10 W each minute. Testing continued until maximal effort (90% maximal predicted heart rate) or a predefined end point was achieved. There were predefined symptomatic, clinical, and ECG criteria for terminating exercise. The reliability of the exercise test in this population was assessed in 9 subjects who completed 2 graded exercise tests 1 week apart. Intraclass correlation coefficients were as follows: maximal heart rate, 0.88; percentage of maximal heart rate, 0.85; peak  $\dot{V}O_2$ , 0.98; metabolic equivalents, 0.84; and exercise duration, 0.94.

### Assessment of Medical Comorbidities

The self-reported Comorbidity Disease Index includes conditions in 8 domains (cardiovascular, pulmonary, endocrine, musculoskeletal, neurological, psychiatric, vision, and cancer) that are relevant to rehabilitation interventions.<sup>31</sup>

### Randomization

After baseline assessments, the subjects were randomly assigned to the intervention or control group through the use of a random-number generator with a block size of 6 and sealed envelopes.

### Blinding

Outcome assessment was performed by research staff blinded to treatment assignment. Participants were instructed to avoid mentioning anything regarding their study experience to the assessors. Participants were not blinded to their assignment but were unaware of the study hypotheses or primary outcome measures.

### Intervention

The exercise program was designed to improve strength, balance, and endurance and to encourage more use of the affected extremity (Table 1). It was supervised by a physical or occupational therapist at home and included 36 sessions of 90-minute duration over 12 to 14 weeks. The intervention group did not receive therapy other than that provided by the study unless they required speech therapy, which was provided outside the study by usual care providers. There were structured protocols for the exercise tasks, criteria for progression, and guidelines for reintroducing therapy after intercurrent illness. The exercises completed during each session were recorded in a treatment log.

### Usual Care

Subjects in the usual care group had services as prescribed by their physicians. Treating therapists for usual care subjects completed a treatment log. Usual care subjects received home visits by research staff every 2 weeks for health education, vital signs, and a test of oxygen saturation.

### Abstraction of Treatment Logs

The intervention and usual care treatment logs were abstracted by 2 trained therapists using a structured abstraction protocol. Interobserver reliability for the log abstraction was assessed in a 10% sample of control logs (n=5) and a 23% sample of intervention logs

**TABLE 1. Components of the Intervention Program**

Range of Motion and Flexibility	Range of motion and stretching to the shoulder, elbow, wrist, fingers, hip, ankle, and trunk
Strengthening	Active motion in PNF unilateral patterns with manual resistance progressing to Theraband repetitions (2 sets of 10) in anatomical planes. Targeted movements for Theraband exercises were shoulder flexion/external rotation, elbow flexion/extension, wrist extension, hip abduction, knee flexion/extension, and ankle dorsiflexion. Once exercise was completed with little difficulty, the resistance of the band used was increased.
Balance	<p>Step-ups: repeated stepping anteriorly and laterally onto a step: up with affected LE and down with unaffected LE, progressing to higher step and decreasing upper extremity support.</p> <p>Chair rises: repeated rising from a seated position, progressing from using arms to not using arms and from high surface to lower.</p> <p>Wall exercise: repetitions of standing from a wall and falling backwards with the trunk straight to contact the wall with the upper back and bouncing upright again, progressing to greater distances from the wall.</p> <p>Marching: repeated marching in place, progressing from UE support to no support.</p> <p>Toe rises: repeated rising up on toes, progressing from UE support to no support and from bilateral rises to unilateral rises on affected LE only.</p> <p>Other: kicking a ball with either foot, simulated batting/golfing, abrupt stops and turns while walking.</p>
UE Functional Use	Practicing the use of the UE in real-life tasks with an emphasis on increasing coordination requirements, eg, washing countertops, opening drawers, putting away dishes, folding towels, closing blinds, counting change, writing.
Endurance	<p>Riding a stationary bike, progressing in time up to 30 min with increasing speed and resistance.</p> <p>Exercise duration was initially increased in 2- to 5-min-increments until 20 to 30 min of continuous cycling at 40 rpm was achieved. Interval training was then instituted and used periods of increased speed to achieve a higher heart rate. Intervals were completed in blocks of 5 minutes (ie, 1-min interval at 50 rpm and 4-min interval at 40 rpm; 1 1/2 min at 50 rpm and 3 1/2 min at 40 rpm; 2 min at 50 rpm and 3 min at 40 rpm). Resistance was increased once the subject could complete 4 2-min intervals. Next phase of endurance training began with continuous cycling at 40 rpm for 25 to 30 min at next level of resistance. Progression continued with interval training as previously described.</p>

PNF indicates proprioceptive neuromuscular facilitation; LE, lower extremity; and UE, upper extremity.

(n=10). Item-level agreement was 98% for control log items and 99% for intervention log items.

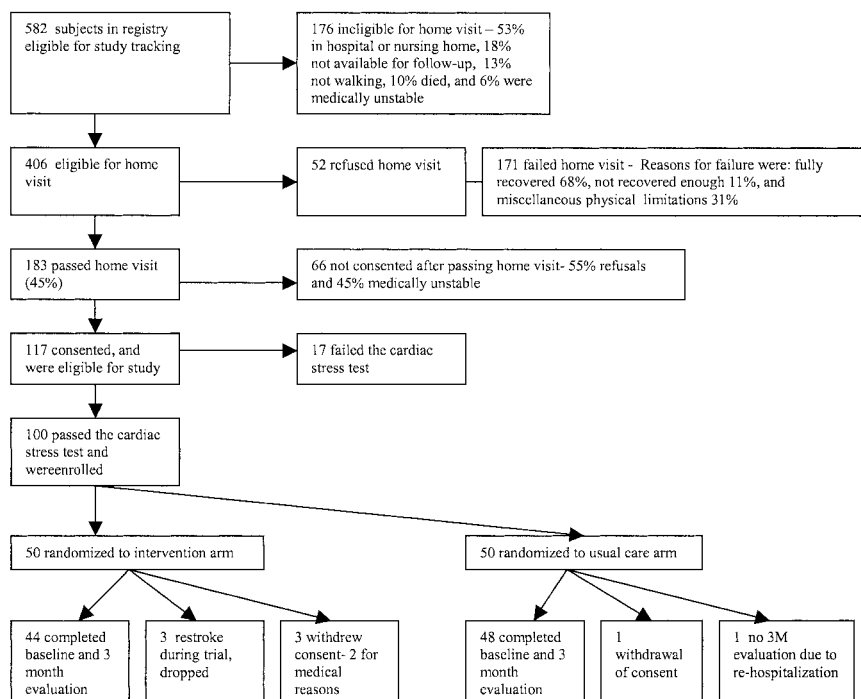
**Adverse Event Monitoring**

This study had a Safety Monitoring Board that reviewed, approved, and monitored the adverse event monitoring and reporting process throughout the study. All subjects were contacted every 2 weeks to discuss adverse events, including healthcare use, medical events, and symptoms.

**Statistical Analysis**

For safety purposes, adverse event rates of the 2 treatment groups were monitored and compared throughout the study using a statistical strategy based on the log rank statistic and conditional power, a methodology suggested by the external safety monitoring committee.

Simple descriptive statistics were used to summarize demographic, stroke, and baseline characteristics. All analyses were performed on an intention-to-treat basis. Any missing values at 3 months were imputed using baseline values, a conservative assumption.



Study flow chart.

**TABLE 2. Baseline Characteristics in 100 Persons With Subacute Stroke Who Entered the Study**

	Intervention Group (n=44)	Usual Care Group (n=48)	Dropouts (n=8) Mean (SD) or N (%)
<b>Demographics</b>			
Age, y	68.5 (9.0)	70.2 (11.4)	74.6 (9.8)
Male sex, n (%)	23 (52.3)	27 (56.3)	6 (75.0)
Race (white), n (%)	37 (84.1)	37 (77.1)	5 (62.5)
Insurance coverage, %			
Medicare	67	61	88
Private	79	90	88
Medicaid	2	2	0
<b>Stroke characteristics</b>			
Orpington Prognostic Score	3.4 (0.8)	3.4 (0.8)	3.4 (0.7)
Stroke location			
Right hemisphere	22 (50.0)	22 (45.8)	3 (37.5)
Left hemisphere	18 (40.9)	22 (45.8)	4 (50.0)
Brain stem/other	4 (9.1)	4 (8.3)	1 (12.5)
Stroke type, ischemic	39 (88.6)	44 (91.7)	7 (87.5)
Time since stroke, d	77.5 (28.7)	73.5 (27.1)	84 (27.2)
<b>Primary outcomes at baseline</b>			
Ankle isometric dorsiflexion, Nm	19.5 (10.0)	20.1 (10.0)	26.2 (7.6)
Knee isometric extension, Nm	59.4 (27.4)	54.8 (22.0)	67.4 (36.2)
Lower-extremity Fugl-Meyer score	24.1 (3.7)	23.7 (3.5)	26.0 (2.9)
Grip strength, kg	15.4 (10.2)	13.4 (9.5)	19.4 (12.1)
Berg Balance Score	42.8 (7.2)	43.1 (9.0)	44.6 (7.9)
Functional reach, cm	25.3 (6.6)	22.3 (6.1)	23.1 (8.0)
Duration of bike exercise, min	5.1 (2.8)	5.2 (2.8)	4.8 (3.3)
Peak $\dot{V}O_2$ , mL · kg <sup>-1</sup> · min <sup>-1</sup>	11.7 (3.3)	11.2 (2.9)	11.1 (3.8)
10-m gait velocity, m/s	0.7 (0.3)	0.6 (0.3)	0.7 (0.2)
6-min walk distance, m	238.0 (103.9)	215.6 (94.8)	244.1 (88.6)
Wolf Motor Function time, s			
Including all subjects*	13.8 (21.9)	12.0 (18.8)	3.4 (1.5)
Excluding those unable to do tasks	3.5 (1.9)	4.5 (2.9)	3.4 (1.5)
Upper-extremity Fugl-Meyer score	45.8 (12.8)	43.3 (11.9)	50.6 (7.4)
<b>Comorbid conditions at baseline, n (%)</b>			
History of angina	5 (11)	3 (6.2)	0
History of heart attack	2 (4.5)	5 (10)	0
Irregular heart rhythm	4 (9.1)	6 (12)	0
High blood pressure	30 (69)	37 (77)	6 (75)
Peripheral vascular disease	4 (9.1)	5 (10)	1 (12)
Lung disease	5 (11)	3 (6.2)	0
Arthritis	19 (43)	22 (46)	6 (75)
Chronic pain	14 (32)	17 (35)	4 (50)
Depression or anxiety	12 (27)	12 (25)	2 (25)
Diabetes	11 (25)	13 (27)	1 (12)

Values are mean ± SD when appropriate.

\* $P < 0.0001$ , those who did vs did not drop out.

tion. In order to protect the type I error rate from multiplicity, a single overall multivariate analysis of variance (MANOVA) was performed using baseline to 3-month change of all primary outcomes. Upon observing statistical significance in MANOVA results, further adjustment for multiplicity was considered unnecessary.<sup>32</sup>

For each of the primary 3-month outcomes, unadjusted univariate *t* tests were performed using baseline to 3-month change, followed by a univariate covariance analysis performed, with treatment group as the primary factor and the baseline measurement as a covariate. Interaction between treatment group and baseline was assessed for

**TABLE 3. Overview of Therapy Received by Usual Care and Intervention Groups**

	Usual Care (n=48)		Intervention, PT and OT Together, (n=44)
	PT	OT	
Unsupervised home exercise program provided, %	60	67	100
Subjects who received therapy visits, n	25	23	44
Site of therapy, n			
Home	3	4	44
Outpatient	20	18	
Both	2	1	
Visits per patient for subjects receiving visits, n	8.7 (5.3)	10.4 (7.1)	33.4 (2.3)
Average duration of visits, min	45.6 (12.2)	47.5 (11.3)	91 (4.5)
Subjects receiving therapy directed at, %			
Strength	50	46	100
Balance	48	14	100
Endurance	12	2	100
Upper extremity	8	42	100
Range of motion	21	37	100
Mobility	50	2	45
ADL/IADL	14	14	16
Progressed in strengthening (of subjects receiving visits), %	28	13	100
Progressed in endurance (of subjects receiving visits), %	4	0	95

PT indicates physical therapy; OT, occupational therapy; ADL, activities of daily living; and IADL, independent ADL. Values in parentheses are SD.

significance for each outcome. If the interaction was significant, a stratified analysis was performed. If not, the analysis was rerun without the interaction term in the covariance model.

**Results**

**Participant Recruitment and Retention**

Five hundred eighty-two subjects in the stroke registry were initially eligible to be followed up (the Figure). Of these, 176 were never eligible for further assessment, 52 refused further screening, and 171 failed clinical eligibility criteria. Of the 183 who met clinical criteria, 30 were medically unstable, and 36 declined to participate in the trial. Of the 117 who agreed to be considered, 17 did not pass the exercise stress test, leaving 100 subjects who were randomized, 50 to each group. Overall, 17% of the Kansas City Stroke Registry subjects who entered study tracking were eligible for randomization.

Ninety-two subjects completed the 3-month posttreatment assessment; 8 dropped out. Six subjects dropped from the intervention arm: 1 had significant renal insufficiency detected after randomization but before therapy; 1 had subclavian steal syndrome diagnosed the first 2 weeks after randomization; 1 chose to withdraw after 18 visits; and 3 experienced a second stroke. Two subjects dropped from the usual care group: 1 withdrew from the study immediately after randomization, and 1 did not return for the 3-month assessment.

The baseline characteristics of the intervention, control, and dropout groups are presented in Table 2. At enrollment, participants were 76±28 days after stroke, were 70±10 years of age, and had moderate stroke deficits (baseline Orpington

Prognostic Score, 3.4±0.8; Fugl-Meyer upper-extremity motor score, 45±12.1; and Fugl-Meyer lower-extremity score, 24±3.6). The baseline maximum exercise capacity was <12 mL · kg<sup>-1</sup> · min<sup>-1</sup>. The 2 treatment arms were comparable in all baseline measures. The subjects who dropped out of the study were older and had less upper-extremity impairment. The participants suffered from many comorbid conditions. Hypertension, diabetes, arthritis, chronic pain, depression and vision problems were common.

**Characteristics of Therapeutic Exercise in the Treatment and Usual Care Groups**

The therapies received by the intervention and usual care groups are described in Table 3. All subjects in the intervention received exercises targeted at strength, endurance, balance, and upper-extremity use. The exercises were protocol driven and included progression of difficulty. Each subject received an average of 33.4±2.3 visits, and the average duration of a visit was 91±4.5 minutes.

In the usual care group, 46% of the subjects did not receive any postacute rehabilitation services from physical or occupational therapy. Two thirds were provided recommendations for an unsupervised exercise program. Among the usual care group members who did receive therapy, participants received an average of 8.7±5.3 physical therapy visits and 10.4±7 occupational therapy visits. Physical and occupational therapy services were received separately as prescribed by their physicians. The total duration of the combined physical and occupational therapy visits in the usual care group was similar to the intervention group (≈90 minutes). The types of services received were categorized into strength,

**TABLE 4. Change in Primary Outcomes From Baseline to 3 Months by Treatment Group**

Primary Outcome	Change From Baseline to 3 Months, mean (SE)		Change From Baseline to 3-Months (a-b)	3-Month Change Adjusted for Baseline
	Intervention (a)	Usual Care (b)		
Ankle isometric dorsiflexion, Nm	1.79 (0.78)	1.83 (0.83)	-0.04 (1.14)	0.02 (1.10)
Knee isometric extension, Nm	7.71 (2.32)	4.12 (2.38)	3.56 (3.32)	5.37§ (3.20)
Lower-extremity Fugl-Meyer score	2.74 (0.46)	1.76 (0.56)	0.98 (0.72)	1.10 (0.68)
Grip strength, kg	2.08 (0.70)	1.76 (0.86)	0.32 (1.10)	0.79 (1.08)
Berg balance score	4.36 (0.71)	1.70 (0.52)	2.66† (0.88)	2.72‡ (0.79)
Baseline below median	6.00 (1.19)	2.21 (0.96)	3.80* (1.54)	4.25† (1.40)
Baseline above median	2.58 (0.57)	1.23 (0.47)	1.35§ (0.74)	1.40§ (0.72)
Functional reach, cm	0.53 (0.69)	0.63 (0.76)	-0.11 (1.02)	0.80 (1.00)
Duration of bike exercise, min	1.39 (0.23)	0.16 (0.20)	1.24‡ (0.30)	1.24‡ (0.31)
Peak $\dot{V}O_2$ , mL · kg <sup>-1</sup> · min <sup>-1</sup>	1.05 (0.23)	0.06 (0.23)	0.99† (0.33)	1.06† (0.32)
10-m gait velocity, m/s	0.18 (0.03)	0.11 (0.02)	0.07§ (0.04)	0.08* (0.04)
6-min walk distance, m	61.61 (9.97)	33.59 (7.33)	28.02* (12.37)	28.21* (12.52)
Wolf Motor Function Test (standard scoring)				
Baseline below median	-0.36 (0.10)	1.42 (1.34)	-1.78 (1.21)	-1.73 (1.23)
Baseline above median	-10.87 (3.13)	-4.78 (2.27)	-6.09 (3.77)	-4.44 (3.29)
Using only subjects completing all tasks				
Baseline below median	-0.30 (0.08)	0.21 (0.29)	-0.51 (0.28)	-0.65* (0.25)
Baseline above median	-1.07 (0.35)	-2.00 (0.49)	0.93 (0.69)	0.48 (0.37)
Upper-extremity Fugl-Meyer score	4.48 (0.81)	4.04 (0.90)	0.44 (1.21)	0.85 (1.16)

\* $P < 0.05$ ; † $P < 0.01$ ; ‡ $P < 0.001$ ; § $0.05 < P < 0.10$ .

balance, endurance, and upper-extremity range of motion/flexibility. Activities that could not be assigned to any of these categories were assigned to the categories of mobility and activities of daily living. There was much variation in the types of exercises received. As conventional practice suggests, physical therapy most often incorporated balance and mobility exercises, and occupational therapy focused on upper-extremity function and range of motion. Endurance training was rarely incorporated into the exercise programs and, if begun, was rarely progressed. Even though strengthening exercises were included in 48% to 50% of physical and occupational therapy programs, strengthening was explicitly progressed in only 13% to 28% of the participants.

### Outcomes at 3 Months

The primary outcomes of the study were assessed at 3 months, immediately after the intervention, and are presented in Table 4. An intention-to-treat analysis was used, with baseline data on dropouts carried forward to estimate 3-month status. The overall effect of the intervention compared with usual care on the combined outcomes was highly significant (Wilk's  $\lambda = 0.64$ ,  $P = 0.0056$ ) by a single multivariate analysis of variance. Both the intervention and usual care groups demonstrated improvements from baseline to 3 months in strength, balance, upper- and lower-extremity motor control, upper-extremity function, and gait velocity. The usual care group did not show gains in endurance. The intervention group achieved greater gains than the usual care group in measures of endurance (peak  $\dot{V}O_2$  and duration of

exercise), balance (Berg Balance Scale), 6-minute walk distance, and gait velocity. Balance gain in the intervention was especially greater in the group with lower initial balance scores. Upper-extremity motor function gains by the Wolf Motor Function Test were greater only in the intervention group with better baseline upper-extremity function. Analyses restricted to the 92 subjects who completed the 3-month evaluation showed similar results (data not shown).

Adverse events were monitored and reported according to the protocol approved by the Safety Monitoring Board. There were no deaths or heart attacks. Event rates never reached predefined stopping criteria. Seven subjects were hospitalized, 4 in the intervention group and 3 in the usual care group. Three subjects, all from the intervention group, had diagnoses of second strokes. Two of the strokes occurred within the first 2 weeks after randomization, and 1 occurred after 7 weeks. No strokes occurred during a treatment session. All 3 subjects were receiving aspirin and presented with nonspecific symptoms of increasing confusion and slurred speech. One was thought to have worsening of existing right-sided weakness. Two of 3 had new radiological evidence of infarct. All 3 returned home.

### Discussion

This 3-month structured, physiologically based, progressive, supervised home-based exercise program improved stroke recovery compared with usual care. Gains were observed in balance, endurance, and mobility. Upper-extremity benefit was limited to participants with better baseline upper-

extremity performance. There were trends toward greater gains in strength and motor control in the intervention compared with the usual care group, but the differences were not significant. The overall benefits of this intervention occurred in individuals who were beyond the 30-day post-stroke period of major recovery who had mild to moderate stroke severity, numerous comorbidities, and low levels of baseline endurance. These results suggest that physiologically based, intensive exercise is effective in improving multiple domains during the subacute phase of stroke recovery and that increased structure, intensity, and progression may be key elements in effective therapy. The benefits found here are specifically noteworthy because the usual care group was also experiencing natural recovery and received prescribed rehabilitation services. The gains from usual care had to be exceeded to detect additional benefit from the intervention.

Gains in endurance with this intervention were comparable to those in previous studies of endurance training in individuals with chronic stroke. Endurance after stroke is compromised to a level that limits basic daily functioning. There were significant gains in fitness, which may help reduce the risk of future decline.

The safety and feasibility of exercising individuals after stroke are concerns. Participants underwent a cardiologist-supervised stress test before the home-based exercise intervention. No major adverse events occurred during exercise sessions. Intercurrent illness and hospitalization were not uncommon in both the intervention and usual care groups. Although there were no deaths or cardiac events, there were 3 recurrent strokes, all in the intervention arm. Reported recurrent stroke rates in the early period after ischemic stroke range from 1.2% to 9%.<sup>33</sup> From the Duke-Port study, the incidence rate for recurrent ischemic stroke was 2.9% at 3 months and 6.0% at 6 months,<sup>33</sup> which is comparable to the intervention arm of our study, which had a 3-month rate of 4.0% and a 6-month rate of 6.0%. We used a stopping rule suggested by the external Safety Monitoring Board based on the log-rank statistic and conditional power to determine whether the difference in recurrent stroke rate across the groups ever implied a meaningful effect. The rate never met the criteria, and continued intervention was recommended by the Safety Monitoring Board. Given the many comorbidities that accompany stroke and the risk of secondary stroke, supervision of exercise training programs is critical. Future studies with larger sample sizes are required to assess the true risk of recurrent stroke with exercise.

This study has several limitations. It was an efficacy study targeted at highly selected subacute stroke and may not be generalizable to all stroke rehabilitation. The intervention is resource intensive. Each subject received a total of 54 hours of 1-on-1 therapy over several months. We do not know what the lowest effective “dose” of intervention might be or whether a more efficient group model intervention might be effective. Our goal was to determine whether a comprehensive, structured, progressive, intensive intervention could achieve important gains. We cannot determine which component of this program contributed (structure, progressive, or intensive) to the successful outcomes. Given the positive

effects found in this study, further efforts to make the intervention more efficient are warranted.

Strength gains in this study did not reach statistical significance. The intervention was supervised and progressive, with Therabands and body weight used for resistance 3 times a week with instructions for unsupervised practice between sessions. Significant improvements in strength may require exercise at a higher intensity.

Motor control gains in the upper and lower extremities were not uniform. Upper-extremity functional gains were limited to those with higher baseline residual upper-extremity capacity. Greater total practice time and repetition, as in constraint-induced therapy models, may be required to influence motor control and function.<sup>13,34</sup> Prior studies demonstrating improved upper-extremity function have been performed in select subjects with volitional upper-extremity, wrist, and finger extension and were based on 6 to 8 h/d of constraint-induced exercise.<sup>13</sup> In contrast, our protocol had only 20 minutes of focused upper-extremity practice per session, with encouragement to practice independently. Optimal gains in upper-extremity function may require more intense repetitive practice and may be limited to those with less severe upper-extremity deficits.

There were no statistical differences in baseline characteristics between the control and intervention groups. However, because of the small sample size, this may be a type II error. Therefore, our assessment of differences between treatment groups was adjusted for baseline values (Table 4).

This was a single-blind study. Exercise interventions are difficult to blind to the recipient. We made efforts to minimize bias by separating the outcome assessors from the interventionists and by providing repeated structured reminders to participants to avoid revealing their treatment status to the assessors. We attempted to offer direct benefit and attention to the usual care group with home visits every 2 weeks for health education and screening. Nevertheless, because participants in the usual care group knew of their treatment assignment, bias in self-reported outcomes could have occurred. A study design with full attentional control would reduce this bias but would not be representative of usual care.

This study was not powered to detect effects on more global functional outcomes. We predefined important end points at the level of impairments and functional limitations with sample size based on power to detect important differences in relevant outcomes such as mobility and balance. To assess effects on more distal outcomes such as disability and quality of life, a large, multisite trial is needed. The study examined outcomes immediately after the intervention. The duration of benefit after therapy requires further study.

## Conclusions

Rehabilitation services for stroke survivors are increasingly constrained by cost concerns, with pressure to discharge individuals from acute rehabilitation earlier when recovery and function have not yet stabilized. This study demonstrates additional functional gains after acute rehabilitation has been completed. These gains are attributable to a structured pro-

gressive program and exceed gains resulting from spontaneous recovery during the subacute phase and usual care.

This intervention was clearly defined, reproducible, and progressive. Its physiological approach was based on integrated functional exercise targeting specific impairments in strength, balance, motor control, and endurance. Usual care in this study was heterogeneous in approach and intensity and demonstrated little evidence for formal progression. To identify potential mechanisms and functional benefits, interventions to promote stroke recovery must be clearly defined. The structured, reproducible intervention proposed here may help to "open the black box" of rehabilitation care and offer patients, therapists, and healthcare systems more specific insight into rehabilitation as an intervention. Persons with subacute stroke may benefit from more highly structured, intensive, and progressive therapeutic exercise. Evidence of gains from intensive therapy in the subacute phase after stroke has substantial implications for future service planning, given the degree of constraint on stroke rehabilitation services in the current healthcare environment.

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